# Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States



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## *Dolutegravir (Tivicay, DTG)*

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### Animal Studies

*Carcinogenicity*

Dolutegravir (DTG) has not been shown to be genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in 2-year, long-term studies in mice at DTG exposures that were up to 14-fold higher than the exposures achieved in humans with systemic exposure to the recommended dose. In addition, no carcinogenicity was detected in rats at DTG exposures up to 10-fold higher in males and 15-fold higher in females than the exposures seen in humans who received the recommended dose.[1]

*Reproduction/Fertility*

DTG did not affect fertility in male and female rats and rabbits at doses that produced exposures (based on area under the curve [AUC]) that were approximately 27-fold higher than that achieved in humans who received the recommended dose.[1]

*Teratogenicity/Adverse Pregnancy Outcomes*

Studies of DTG in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity, or effects on reproductive function.[1]

*Placental and Breast Milk Passage*

Studies in rats have demonstrated that DTG crosses the placenta and is excreted into breast milk.[1]

### Human Studies in Pregnancy

*Pharmacokinetics*

DTG pharmacokinetics (PK) in human pregnancy have been reported in three studies and a series of case reports.[2-8] In a safety and PK study of 29 pregnant women in the United States, DTG plasma concentrations were lower during pregnancy than postpartum, with DTG AUC reduced by 21% during pregnancy. Although trough concentrations were reduced by 34% during the third trimester compared to postpartum, trough concentrations during pregnancy were well above 0.064 μg/mL, the 90% effective concentration for DTG. DTG was well tolerated by these pregnant women. During the third trimester, HIV-1 RNA was below 50 copies/mL in 27 of 29 participants, and no infants acquired HIV.[7]

In contrast, PK sampling during pregnancy and the early postpartum period of 17 African women who were receiving DTG showed a small reduction in DTG $C_{max}$ and no differences in $C_{24h}$ and $AUC_{0\text{-}24h}$ when geometric mean ratios in pregnancy were compared to the postpartum period. However, postpartum sampling was performed at a median of 10 days postpartum, when maternal physiology had likely not yet returned to the nonpregnant state.[8] In a smaller study of five European pregnant women, DTG was well tolerated and the reduction in plasma exposures during pregnancy was similar to that observed in the U.S. study described above.[6] In the case reports, DTG was used safely and effectively in individual pregnant women and plasma exposures were adequate.[2-5]

*Placental and Breast Milk Passage*

Placental transfer of DTG in an *ex vivo* perfusion model was high, with a mean fetal-to-maternal concentration ratio of 0.6.[9] In two *in vivo* PK studies, the median DTG cord blood-to-maternal-plasma concentration ratios were 1.21 and 1.25.[7,8] High placental transfer of DTG has also been reported in several of the case reports.[2,4,5] In 17 breastfeeding mothers, the median ratio of DTG in breast milk to maternal plasma was 0.03. Their infants had a median maximum DTG concentration of 66.7 ng/mL (range 21–654 ng/mL) and a median minimum concentration of 60.9 ng/mL (range 16.3–479 ng/mL) at a median age of 10 days (range 7–18 days). The geometric mean ratio of infant plasma to maternal plasma DTG concentrations in these 17 mother-infant pairs was 0.03.[8]

*Teratogenicity/Adverse Pregnancy Outcomes*

Among live births that have been reported to the Antiretroviral Pregnancy Registry as of January 31, 2019, the overall birth defect rate for infants with first-trimester exposure to DTG is 3.6% (11 infants out of 302 live births).[10] There has been one neural tube defect (NTD) among the 248 infants with periconception exposure to DTG that have been reported to the Antiretroviral Pregnancy Registry.[10] In the U.S. PK study in pregnant women discussed above, birth abnormalities were reported in seven of 29 infants: three with normal variants; one with total anomalous pulmonary venous return (DTG was initiated at 16 weeks gestation); one with a polycystic right kidney (DTG was initiated at 11 weeks gestation); one with an isolated left renal cyst (DTG was initiated at 12 weeks gestation); and one with jitteriness and chin tremors (DTG was initiated at 28 weeks gestation).[7] DTG was initiated at 28 weeks gestation or later in the PK study in African women discussed above, and no congenital anomalies were observed among 28 live births.[8] In two reviews of clinical experience with pregnant women who received DTG, birth defects were noted in four infants born to 81 European women, in two infants born to 66 women from the United States, and in no infants born to 116 women from Botswana who received DTG during the first trimester.[11-13]

In July 2019, a report from a National Institutes of Health-funded surveillance study of birth outcomes among pregnant women in Botswana who were receiving antiretroviral therapy found that DTG exposure at the time of conception was associated with a slightly higher rate of NTDs than other types of antiretroviral drug exposure (0.3% vs. 0.1%).[14] Unlike in the United States, there is no folate fortification of food in Botswana, and it is unknown how folate levels may affect the possible association between periconceptual DTG exposure and NTDs. The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission recommends the use of DTG as part of a *Preferred* regimen in all pregnant women at any gestational age and as part of an *Alternative* regimen in women who are trying to conceive. Decisions about DTG use should be made after discussing the risks and benefits of using DTG with the patient. This discussion should include the potential risk of NTDs, as well as the benefits of the DTG-containing regimen and the risks and benefits of alternative regimens (see Appendix D: Dolutegravir Counseling Guide for Health Care Providers). For additional information, please contact the National Perinatal HIV Hotline (1-888-448-8765) and see Updated Guidance About the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy and Teratogenicity.

## Excerpt from Table 8

**Note:** When using FDC tablets, refer to other sections in Appendix B and Table 8 for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

| **Generic Name** (Abbreviation) *Trade Name* | **Formulation** | **Dosing Recommendations**[a] | **Use in Pregnancy** |
|---|---|---|---|
| **Dolutegravir** (DTG) *Tivicay*<br><br>(DTG/3TC) *Dovato*<br><br>(DTG/RPV) *Juluca*<br><br>(DTG/ABC/3TC) *Triumeq* | **DTG (Tivicay):**<br>• DTG 50 mg tablet<br><br>**DTG/3TC (Dovato):**<br>• DTG 50 mg/3TC 300 mg tablet<br><br>**DTG/RPV (Juluca):**<br>• DTG 50 mg/RPV 25 mg tablet<br><br>**DTG/ABC/3TC (Triumeq):**<br>• DTG 50 mg/ABC 600 mg/3TC 300 mg tablet | **Standard Adult Doses**<br>*In ARV-Naive or ARV-Experienced (but INSTI-Naive) Patients*<br>DTG (Tivicay):<br>• One tablet once daily, without regard to food<br><br>DTG/3TC (Dovato):<br>• One tablet once daily, without regard to food<br><br>DTG/RPV (Juluca):<br>• One tablet once daily with food<br><br>DTG/ABC/3TC (Triumeq):<br>• One tablet once daily, without regard to food<br><br>*In ARV-Naive or ARV-Experienced (but INSTI-Naive) Patients Who Are Also Receiving EFV, FPV/r, TPV/r, or Rifampin*<br>DTG (Tivicay):<br>• One tablet twice daily, without regard to food<br><br>*In INSTI-Experienced Patients*<br>DTG (Tivicay):<br>• One tablet twice daily, without regard to food<br><br>**Pregnancy**<br>*PKs in Pregnancy:*<br>• AUC may be decreased during the third trimester compared with postpartum, but exposures during pregnancy are well above those needed to inhibit viral replication.<br><br>*Dosing in Pregnancy:*<br>• No change in dose indicated.<br>• For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC, RPV). | High placental transfer to fetus.[b]<br><br>No evidence of teratogenicity in rats or rabbits. In pregnancy surveillance data from Botswana, there was a slightly increased risk of NTDs in infants born to women who initiated DTG prior to pregnancy and who were receiving it at the time of conception.<br><br>DTG may be used as part of a *Preferred* regimen in all pregnant women at all gestational ages and as part of an *Alternative* regimen in women who are trying to conceive. Clinicians should discuss the risks and benefits of DTG use with the patient. For more information, see Updated Guidance About the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy.<br><br>To maximize DTG absorption, doses should not be administered within 2 hours of ingesting any preparation that contains minerals such as iron or calcium, including prenatal vitamins. |

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

**High:** >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

**Key:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; AUC = area under the curve; DTG = dolutegravir; EFV = efavirenz; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; PK = pharmacokinetic; RPV = rilpivirine; TPV/r = tipranavir/ritonavir

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